REMARKS

1. STATUS OF THE CLAIMS

Claims 1, 3, 6, 8-23 and 25-33 are pending.

Claim 3 has been amended to change its form from a dependent to an independent claim by incorporating limitations from Claim 1, from which it depended.

Claims 6, 8-23, 25-26, 27-34 have been withdrawn from consideration as being directed to a non-elected invention. In view of the inadvertent occurrence of two claims numbered as claim 26, the second occurrence of claim 26 has been re-numbered as claim 27. Also, pending mis-numbered Claims 27-34 have been renumbered as Claims 28-35 to maintain sequential claim numbering, as proposed by the Examiner.[1] Reference within the text of the newly numbered Claims 28-35 has also been corrected to reflect the correct re-numbering of the claims.

Applicants' amendments do not introduce new matter.

2. ELECTION

Applicants affirm their election of **Group I,** Claims 1 and 3, drawn to a method of identifying a test agent capable of reducing macrophage apoptosis involving protein kinase R, and election of the species of "***Salmonella species,***" without traverse.[2]

3. REQUEST REJOINDER OF SPECIES

Applicants respectfully request rejoinder and consideration, upon allowance of a **generic** claim, of non-elected **species** claims that depend from or requires all the limitations of the allowable **linking genus claims,** as provided by 37 CFR § 1.141 and MPEP 809,[3] including any claims that may have been previously withdrawn from consideration, such as the species of bacterium selected from the group consisting of *Bacillus species, Yersinia species, Shigella species, Streptococcus species* and *Haemophilus species*, as recited in Claims 20 and 31. Indeed,

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1 Office Action, page 2, item 2.

2 Office Action, page 2, item 1.

3 "... linking claims which, if allowable, act to prevent restriction between inventions that can otherwise be shown to be divisible, are (A) genus claims linking species claims; and (B) subcombination claims linking plural combinations." MPEP 809. Also, "Any claim(s) directed to the nonelected invention(s), previously withdrawn from consideration, which depends from or requires all the limitations of the allowable linking claim must be rejoined and will be fully examined for patentability." MPEP 809.

the Examiner's statements in the prior Office Action mailed on October 26, 2008 concede Applicants' right to rejoinder.[4]

4. REJECTION OF CLAIM 1 UNDER 35 U.S.C. §102(b) OVER WARING

Claim 1 stands rejected for alleged anticipation under 35 U.S.C. §102(b) over Waring.[5, 6] Applicants respectfully disagree because Waring does not disclose the recited step c) of "detecting reduced activity of protein kinase R." Under the law,

> "Anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration."[7] The corollary to that is that "absence from the reference of any claimed element negates anticipation."[8]

Waring discloses the effect of the protein synthesis inhibitors cycloheximide, actinomycin D, and ricin on macrophage cell apoptosis that is induced by treatment of macrophages with gliotoxin. Waring also discloses that "DNA fragmentation [is] characteristic of apoptosis in macrophages."[9] In view of the correlation between DNA fragmentation and apoptosis, Waring measures the level of DNA fragmentation to determine the level of apoptosis.[10]

The Examiner argued that Waring's measurement of DNA fragmentation is the same as the recited "detecting reduced activity of Protein Kinase R" on the basis that Waring's measurement of DNA fragmentation is "taught by Applicant as being sufficient to measure PKR-induced apoptosis."[11] This reflects a misunderstanding of the Specification. The Specification teaches that DNA fragmentation is a measure of **apoptosis**, not of the recited "activity of Protein Kinase R." More specifically, the Specification teaches

> "For example, **apoptosis** may be determined by techniques for detecting **DNA fragmentation**, (for example any version of the Terminal deoxynucleotidyl transferase (TdT)-mediated dUTP Nick End-Labeling TUNEL technique

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4 Office Action mailed on October 26, 2008, page 4, first paragraph.
5 Waring, (1990) J. Biol. Chem, 265:14476-14480.
6 Office Action, page 3, item 3.
7 *W.L. Gore & Assoc., Inc v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303, 313 (Fed. Cir. 1983), cert. denied, 105 S. Ct. 172 (1984), citing *Soundscriber Corp. v. U.S.*, 360 F.2d 954, 960, 148 USPQ 298, 301, adopted, 149 USPQ 640 (Ct. Cl. 1966).
8 *Rowe v. Dror*, 42 USPQ2d 1550, 1553 (Fed. Cir. 1997), citing Kloster Speedsteel AB v. Crucible, Inc., 793 F.2d 1565, 1571, 230 USPQ 81, 84 (Fed. Cir. 1986).
9 Waring, page 14476, 2nd column, 1st paragraph.
10 Waring, pages 14477-14479, "Results."
11 Office Action, page 3, item 3.

> originally developed by Gavrieli *et al.* J Cell Biol. 1992 Nov;119(3):493-501, nuclear staining with nucleic acid dyes such as Hoechst 33342, Acridine Orange and the like, and detecting DNA "ladder" fragmentation patterns associated with apoptosis (*e.g.* DNA gels and the like)). In one embodiment, apoptosis is measured by TUNEL (for example, Park *et al.* Science 297, 2048-51, 2002). In one embodiment **apoptosis** is measured by observing **DNA fragmentation** in a ladder pattern (for example, Park *et al.* Science 297, 2048-51, 2002)."

Because the Examiner misunderstood the meaning of Applicants' teachings in the Specification, the Examiner's basis for equating Waring's measurement of DNA fragmentation with the recited activity of Protein Kinase R is erroneous. Accordingly, Applicants respectfully request withdrawal of the rejection of Claim 1 for alleged anticipation under 35 U.S.C. §102(b) over Waring.

5. REJECTION OF CLAIMS 1 AND 3 UNDER 35 U.S.C. §103(a) OVER WARING, JESENBERGER *et al.* AND LIU *et al.*

Claims 1 and 3 have been rejected for alleged obviousness under 35 U.S.C. §103(a) over Waring, Jesenberger *et al.*[12] and Liu *et al.*[13, 14] Applicants respectfully traverse. Under the law, an invention "might" be obvious if (a) each element was, independently, known in the prior art, **and** (b) there is a finite number of identified predictable solutions that include the claimed invention.[15] Failure to establish either of these requirements negates obviousness. Indeed, the prior art does not suggest either of the above requirements, thus necessitating withdrawal of the rejection. This is further discussed below.

A. The prior art does not disclose Claim 3's limitation of "anti-bacterial"

The Supreme Court affirmed that the threshold requirement for finding obviousness is "demonstrating that each element was, independently, known in the prior art."[16] The Examiner **admitted** that "Waring does **not** teach identification of apoptosis inhibitors as antibiotics."[17] Indeed, none of the remaining cited references teaches or suggests an "anti-bacterial" agent

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12 Jesenberger *et al.* (2000) J. Expt. Med. 192:1035-1045.
13 Liu *et al.* (2001) J. Virology 75:6402-6409.
14 Office Action, page 4, item 4.
15 *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398, 127 S.Ct. 1727, 82 USPQ2d 1385, (2007).
16 *Id.*
17 Office Action, page 4, last full paragraph.

because they each relate to **viruses, not to bacteria**. Because this threshold requirement is lacking with respect to Claim 3, this claim cannot be obvious. Therefore, Applicants respectfully request withdrawal of the rejection of Claim 3 for alleged obviousness.

B. <u>The prior art does not suggest a "finite number of identified predictable solutions" that include the claimed methods of Claims 1 and 3</u>

An essential element in establishing that an invention "might" be obvious is providing evidence that "there are a finite number of identified predictable solutions" to a prior art problem, and that the solutions include the claimed invention.[18] However, the prior art suggests a large universe of possible solutions without guidance on what to pick and choose, and without guidance on how to reasonably predict that the claimed methods would succeed.

In particular, Waring discloses the effect of the protein synthesis inhibitors cycloheximide, actinomycin D, and ricin on macrophage cell apoptosis that is induced by treatment of macrophages with gliotoxin. Waring makes no reference whatsoever to Protein Kinase R, much less to Claim 1's recited "reduced activity of Protein Kinase R."

Similarly to Waring, Jesenberger *et al.* does not disclose "reduced activity of Protein Kinase R." In particular, Jesenberger *et al.* discloses that macrophage apoptosis that is caused by *Salmonella typhimurium* infection involves activation of the protease caspase-2.[19] This disclosure is limited to caspase-2, **without** any suggestion of the involvement of the recited "protein kinase R" in "apoptosis of macrophage cells."

Liu *et al.* discloses that Vero cells infected with infectious bronchitis virus (IBV) undergo "[c]aspase-dependent apoptosis"[20] and that apoptosis is inhibited by the "general caspase inhibitor z-VAD-FMK."[21] Importantly, however, Liu *et al.*'s data was obtained using Vero cells, **not** the recited "macrophage cells." Thus, Liu *et al.* does not disclose that reducing the activity of PKR results in reducing apoptosis in the recited "macrophage cells."

The Examiner attempted to overcome the deficiencies of both Jesenberger *et al.* and Liu *et al.* by combining their disclosures, and arguing that Liu *et al.* discloses that "the involvement

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18 *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398, 127 S.Ct. 1727, 82 USPQ2d 1385, (2007).

19 Jesenberger *et al.*, Abstract; "Capsase-2 Inhibition Delays Apoptosis In Both wt and Caspase-1-deficient Macrophages," page 1041; Discussion, page 1042-1043.

20 Liu *et al.*, Abstract.

21 Liu *et al.*, "Inhibition of IBV-induced apoptosis but not productive replication of IBV in Vero cells by the general caspase inhibitor z-VAD-FMK," page 4605.

of microbial and non-microbial proapoptotic entities in Caspase-dependent PKR mediated apoptosis was well known in the microbial arts."[22] The Examiner's position is **contradicted** by Liu *et al.*, which shows that caspase-dependent apoptosis does **not** involve PKR. In particular, Liu *et al.* teaches that although caspase-dependent apoptosis was observed when Vero cells were infected with IBV, nonetheless, there was

> "**No** obvious increase of the phosphorylation of PKR at the time of apoptosis detected was observed (data not shown), **ruling out the possibility that activation of PKR may contribute significantly to the induction of apoptosis** during IBV infection."[23]

In other words, Liu *et al.* demonstrates that the method of independent Claim 1 is **unpredictable**, because Liu *et al.* shows that **apoptosis does not necessarily involve PKR.**

Moreover, the Examiner appears to have impermissibly "simply retraced the path of the inventor with hindsight, [and] discounted the **number and complexity of the alternatives**," a practice that was recently warned against by the Federal Circuit.[24] In particular, the prior art (*e.g.*, O'Brien[25] at Tab 1) cited by Liu *et al.* suggests several potential classes of cellular molecules, other than PKR, that are involved in cell apoptosis, including p53, Bax, Caspases, cellular IAPs, and Death Domain protein signaling complexes (TRAFs).[26] This means that one of skill in the art who is faced with Liu *et al.*'s and O'Brien *et al.*'s disclosures would have had to screen each of the **at least 6 classes of cellular molecules** disclosed by O'Brien and Liu *et al.* as potential apoptosis targets in each of an extensive universe of **cells**, exemplified by the enclosed list of approximately **210 cell types** (Tab 2), in order to **empirically** determine which class(es) of cellular molecules plays a role in apoptosis of each of those cells. Thus, even without including the different sub-types within each of the classes of cellular molecules that are disclosed by O'Brien, (*e.g.*, the class of capases that includes the sub-types of caspase-1, caspase-2, caspase-3, caspase-4, caspase-5, caspase-6, caspase-7, caspase-8, caspase-9, caspase-10, caspase-11, caspase-12, caspase-13, and caspase-14; the class of TRAFs that includes TRAF1, TRAF2, TRAF3, TRAF4, TRAF5, and TRAF6; *etc.*), the artisan was faced with

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22 Office Action, page 5, 1st paragraph, citing Liu *et al.* page 6407-08, "Discussion."
23 (Emphasis added) Liu *et al.*, page 6408, 1st column, 1st paragraph.
24 *Ortho-McNeil Pharmaceutical Inc. v. Mylan Laboratories Inc.*, 520 F.3d 1358 (Fed. Cir. 2008).
25 O'Brien. 1998. Viruses and apoptosis. J. Gen. Virol. 79:1833-1845.
26 O'Brien, Fig. 1

screening **at least 1,260 combinations**[27] of cells and cellular molecules. Not only would the artisan have had to **screen** a large number of alternative target cellular molecules and pathways in a large number of cells as potential research avenues, but the ordinarily skilled artisan would also have to have some **reason to select** (among several unpredictable alternatives) the exact route (*i.e.*, the recited "Protein Kinase R") that produced the recited "apoptosis" in a particular cell type (*i.e.*, the recited "macrophage cells." This clearly is **not** the easily traversed, small and finite number of alternatives that *KSR* suggested might support an inference of obviousness.[28]

C. The prior art does not suggest that the "antibiotic" activity recited in Claim 3 is "predictable"

Even if, for the sake of argument and without conceding that, the artisan may have deduced that agents that reduced PKR activity also reduced apoptosis in macrophage cells, the artisan nonetheless would not reasonably predict Claim 3's "anti-bacterial" activity. Indeed, Liu *et al.* teaches away from this activity. In particular, Liu *et al.* shows that inhibiting cellular apoptosis does **not** necessarily reduce infection. It says:

> "Furthermore, **inhibition** of IBV-induced **apoptosis** by the general caspase inhibitor x=VAD-FMK **marginally affects the replication and accumulation of IBV**."[29]

In other words, even beyond the above-discussed screening and selecting, the ordinary artisan in the field would also have had to proceed in a direction that is **diametrically opposite** from that in Liu *et al.*, which unequivocally demonstrated failure to inhibit infection by reducing cell apoptosis. Furthermore, the uncertainty faced by the ordinary skilled artisan is not only the result of Liu *et al.*'s failure to demonstrate a causative link between reducing cell apoptosis and reducing infection, but is also compounded by the fact that Liu *et al.*'s data relates only to a **single virus** in **Vero cells** whereas Claim 3 recites "antibacterial" activity that is directed to **several bacterial species** by targeting **macrophage cells**. These distinction with respect to both the pathogen (virus compared to bacteria) and cell type (epithelial Vero cells compared to macrophage cells) are important; none of the references provides **any scientific basis or**

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27 Combining 6 molecule classes with each of 210 cell types yields 1,260 combinations.

28 *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398, 127 S.Ct. 1727, 82 USPQ2d 1385, (2007). See also Ortho-McNeil Pharmaceutical Inc., v. Mylan Laboratories Inc., 520 F.3d 1358 (Fed. Cir. 2008).

29 (Emphasis added) Liu *et al.*, page 6403, 1st column, 1st paragraph.

guidance on extrapolating from Liu *et al.*'s data with viruses to the recited bacteria. Indeed, correlating the effect of Liu et al.'s virus to the claim's "antibacterial" activity would be untenable because of the differences between the biology of virus infection and of bacterial infection. For example, Liu et al.'s Vero cells act as the host cells for infectious bronchitis virus (IBV) that triggers their apoptosis in order to

> "facilitate the spread of virus progeny to the neighboring cells and to minimize the inflammatory reaction evoked by virus-infected cells on the host."[30]

This is in contrast to bacterial infection, wherein bacteria do **not** replicate inside the recited "macrophage cells" and do not use these cells for propagation of their progeny. Said differently, because the biology of viral and bacterial infections is distinct, there is no scientific basis for extrapolating the mechanisms underlying viral infection to bacterial infection. Rather, faced with uncertainty at various stages of their research, the inventors' results were **empirically** determined.

In sum, the prior art fails to teach all the elements of Claim 3, and also fails to provide a finite number of identified predictable solutions that include the invention of Claims 1 and 3. Accordingly, Applicants respectfully request withdrawal of the rejection of Claims 1 and 3 for alleged obviousness under 35 U.S.C. §103(a).

CONCLUSION

Applicants respectfully request reconsideration of the application in view of the above, which places the claims in condition for allowance. To expedite prosecution, Applicants also

[30] Liu et al. , page 6408, 2nd column, 2nd paragraph.

respectfully invite the Examiner to **call the undersigned before drafting another written communication**, if any.

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